Frequently asked questions
Find information on the efficacy and safety of EXPAREL in interscalene brachial plexus nerve block, as well as guidance on administration.

<table>
<thead>
<tr>
<th>Question</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>What is EXPAREL?</td>
<td></td>
</tr>
<tr>
<td>What is the indication for EXPAREL in nerve block?</td>
<td></td>
</tr>
<tr>
<td>What was the study design of the pivotal trial of EXPAREL for interscalene brachial plexus nerve block?</td>
<td></td>
</tr>
<tr>
<td>What were the efficacy results for the pivotal study of EXPAREL for interscalene brachial plexus nerve block?</td>
<td></td>
</tr>
<tr>
<td>What was the impact of EXPAREL on opioid use in the interscalene brachial plexus nerve block study?</td>
<td></td>
</tr>
<tr>
<td>Were any patients opioid free in the pivotal study of EXPAREL for interscalene brachial plexus nerve block?</td>
<td></td>
</tr>
<tr>
<td>What were the safety results for EXPAREL in the pivotal interscalene brachial plexus nerve block study and overall in nerve block?</td>
<td></td>
</tr>
<tr>
<td>Was there any phrenic nerve involvement noted in the interscalene brachial plexus nerve block trial?</td>
<td></td>
</tr>
<tr>
<td>Were symptoms of Horner’s Syndrome noted in the interscalene brachial plexus nerve block trial?</td>
<td></td>
</tr>
<tr>
<td>What is the incidence of paresthesia seen in the interscalene brachial plexus nerve block trial of EXPAREL?</td>
<td></td>
</tr>
<tr>
<td>What was the onset of action of EXPAREL in the interscalene brachial plexus nerve block trial?</td>
<td></td>
</tr>
</tbody>
</table>
### Frequently asked questions continued

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>How long did sensory blockade and motor blockade last with EXPAREL in interscalene brachial plexus nerve block?</td>
<td></td>
</tr>
<tr>
<td>Is the plasma concentration of bupivacaine directly related to pain relief or motor function?</td>
<td></td>
</tr>
<tr>
<td>How long can plasma levels of bupivacaine persist after administration of EXPAREL for interscalene brachial plexus nerve block?</td>
<td></td>
</tr>
<tr>
<td>When administering EXPAREL for interscalene brachial plexus nerve block, will plasma levels of bupivacaine reach neurotoxic levels?</td>
<td></td>
</tr>
<tr>
<td>Can I use 20 mL of EXPAREL for an interscalene brachial plexus nerve block?</td>
<td></td>
</tr>
<tr>
<td>Can bupivacaine HCl be mixed with EXPAREL in a nerve block?</td>
<td></td>
</tr>
<tr>
<td>Why should I not exceed a 1:2 ratio of bupivacaine to EXPAREL when admixing?</td>
<td></td>
</tr>
<tr>
<td>How do I factor in the amount of bupivacaine in EXPAREL into my weight-based bupivacaine calculations?</td>
<td></td>
</tr>
<tr>
<td>Can I administer other local anesthetics after using EXPAREL for interscalene brachial plexus nerve block?</td>
<td></td>
</tr>
<tr>
<td>Can a surgeon infiltrate with EXPAREL if an interscalene brachial plexus nerve block with EXPAREL is performed? In other words, can EXPAREL be used as infiltration and for interscalene brachial plexus nerve block in the same patient?</td>
<td></td>
</tr>
</tbody>
</table>
**What is EXPAREL?**

EXPAREL is an FDA-approved, long-lasting nonopioid analgesic that is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks. More than 6 million patients have received nonopioid EXPAREL since 2012. EXPAREL works locally at the surgical site and uses the DepoFoam® drug delivery technology, which encapsulates bupivacaine in multivesicular liposomes. After injection, DepoFoam® particles gradually release bupivacaine over time, as the lipid membranes are absorbed, prolonging the duration of action of bupivacaine. EXPAREL has been studied in a pivotal trial for interscalene brachial plexus nerve block.

**What is the indication for EXPAREL in nerve block?**

EXPAREL is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks.
What was the study design of the pivotal trial of EXPAREL for interscalene brachial plexus nerve block?

The trial of EXPAREL for interscalene brachial plexus nerve block was a phase 3, multicenter, randomized, double-blind, placebo-controlled study, which was conducted at 17 sites across the United States, Belgium, and Denmark. This study included 140 adult patients (EXPAREL, n=69; placebo, n=71) scheduled to undergo total shoulder arthroplasty or rotator cuff repair. Patients were randomized (1:1) to receive a single dose of EXPAREL 133 mg or placebo, both at a volume of 20 mL. Study treatments were administered as an ultrasound-guided interscalene brachial plexus nerve block 1 hour before the surgical procedure as part of a standardized, multimodal pain management protocol.

The primary efficacy endpoint for this study was the area under the curve (AUC) of the pain intensity score, a measure of cumulative pain, from the first pain assessment after surgery through 48 hours. For the primary efficacy endpoint, pain intensity was evaluated using a 10 cm visual analog scale (VAS), where 0 cm = no pain and 10 cm = worst possible pain. Secondary efficacy endpoints were intended to evaluate opioid use and included analyses of total postsurgical opioid consumption through 48 hours, the percentage of opioid-free patients through 48 hours, and the time to first opioid rescue through 48 hours.
What were the efficacy results for the pivotal study of EXPAREL for interscalene brachial plexus nerve block?

The primary efficacy endpoint of the FDA-approval phase 3 study of EXPAREL for interscalene brachial plexus nerve block was met. Cumulative pain scores were significantly lower in the EXPAREL 133 mg dose group compared with the placebo group through 48 hours. The AUC of pain intensity scores (on a VAS) at 48 hours was 136 for EXPAREL and 254 for placebo (least-squares mean difference, −118; \( P < .0001 \)). This reduction in pain intensity was observed throughout the first 48 hours after surgery, with mean VAS scores of approximately 5 to 7 for the placebo group and 2 to 3 for the EXPAREL group.\(^4\)

[Graph showing pain intensity scores over time, with EXPAREL showing significantly lower pain reduction compared to placebo.]
What was the impact of EXPAREL on opioid use in the interscalene brachial plexus nerve block study?

Through the first 48 hours after shoulder surgery, a significant 78% reduction in opioid consumption was observed with EXPAREL compared with placebo. On average, patients in the EXPAREL group received a total of 12.0 morphine-equivalent units (MEU) of opioids, while patients in the placebo group received an average of 54.3 MEU. Further, the median time to the first use of opioid medication was significantly longer with EXPAREL (4 hours) than with placebo (35 minutes; \( P < .0001 \)).

The clinical benefit in the decrease in opioid consumption was not demonstrated in the pivotal trials.

Back to questions
Were any patients opioid free in the pivotal study of EXPAREL for interscalene brachial plexus nerve block?

A significantly higher proportion of patients in the EXPAREL group did not use any opioid rescue medications through 48 hours after surgery compared with the placebo group \((P=0.008)\).\(^4\)

![Bar chart showing percentage of patients opioid free over time.](chart.png)
FAQs

What were the safety results for EXPAREL in the pivotal interscalene brachial plexus nerve block study and overall in nerve block?

In the pivotal interscalene brachial plexus nerve block trial, EXPAREL was well tolerated, with rates of adverse events that were generally comparable to those observed in the placebo group. Adverse events that occurred in ≥5% of patients in the EXPAREL 133 mg group in the interscalene brachial plexus nerve block trial were nausea, headache, constipation, dysgeusia, pyrexia, hypoesthesia, muscle twitching, vomiting, pruritus, dizziness, hypertension, and dyspepsia.

Overall, the safety of EXPAREL (133 or 266 mg) for nerve block was evaluated in 4 randomized, double-blind, placebo-controlled clinical studies, which included 469 patients undergoing various surgical procedures. Across these 4 studies, the most common adverse reactions (incidence ≥10%) following EXPAREL administration were nausea, pyrexia, and constipation.

Was there any phrenic nerve involvement noted in the interscalene brachial plexus nerve block trial?

No adverse events (dyspnea, poor oxygen saturation) indicative of phrenic nerve involvement were observed in the interscalene brachial plexus nerve block trial of EXPAREL. Of note, dyspnea was designated as an adverse event of special interest in the interscalene brachial plexus nerve block trial and was closely monitored by the investigators.

Were symptoms of Horner’s Syndrome noted in the interscalene brachial plexus nerve block trial?

There were no signs or symptoms (eg, partial ptosis, anhidrosis, miosis) of Horner’s syndrome reported in the study.

Back to questions
What is the incidence of paresthesia seen in the interscalene brachial plexus nerve block trial of EXPAREL?

In the interscalene brachial plexus nerve block trial, the incidence of paresthesia was 1.4% in patients receiving 133 mg of EXPAREL and 1.4% in those receiving placebo.4

What was the onset of action of EXPAREL in the interscalene brachial plexus nerve block trial?

In the brachial plexus trial, patients began to lose sensitivity to cold, pinprick, and light touch in the distal part of innervated dermatomes (musculocutaneous, median, ulnar, radial, and axillary) within 30 minutes after administration of EXPAREL 133 mg.4

How long did sensory blockade and motor blockade last with EXPAREL in interscalene brachial plexus nerve block?

The median time to return of sensory function with EXPAREL was 36 hours.4 Sensory loss was assessed by testing for the absence of sensation (cold, pinprick, or light touch) in the distal part of the innervated dermatomes (musculocutaneous, median, ulnar, radial, or axillary).4

The median time to return of motor function was 24 hours with EXPAREL.4 Motor function was assessed by measuring change from baseline in thumb abduction (radial nerve), thumb adduction (ulnar nerve), thumb opposition (median nerve), and elbow flexion (musculocutaneous nerve).4

It is important to remember that the efficacy of EXPAREL is based on pain relief, as assessed by the AUC of the VAS scores through 48 hours. As shown by the primary endpoint in the interscalene brachial plexus nerve block trial, EXPAREL provided prolonged pain relief, although sensory function returned within 36 hours and motor function within 24 hours.4
Is the plasma concentration of bupivacaine directly related to pain relief or motor function?

With respect to pain relief, systemic plasma levels of bupivacaine cannot be correlated with the local efficacy of EXPAREL at the site of the interscalene brachial plexus nerve block. Likewise, a correlation between systemic plasma bupivacaine levels and the impact of EXPAREL motor function cannot be made, as demonstrated by the fact that the time to reach the maximum plasma concentration (T\text{max}) of bupivacaine occurred at 48 hours, while motor function returned within 24 hours.\textsuperscript{4}

How long can plasma levels of bupivacaine persist after administration of EXPAREL for interscalene brachial plexus nerve block?

Systemic plasma levels of bupivacaine can persist for 120 hours after interscalene brachial plexus nerve block.

When administering EXPAREL for interscalene brachial plexus nerve block, will plasma levels of bupivacaine reach neurotoxic levels?

The C\text{max} for bupivacaine with EXPAREL in the interscalene brachial plexus nerve block trial (mean, 207 ng/mL) was below the concentrations reported to elicit early subjective central nervous system (CNS) toxicity symptoms (2,500 to 4,000 ng/mL) and below the reported lower threshold for toxicity of 800 ng/mL.
Can I use 20 mL of EXPAREL for an interscalene brachial plexus nerve block?

The recommended dose of EXPAREL for interscalene brachial plexus nerve block in adults is 133 mg (10 mL) and is based on the pivotal study of patients undergoing either total shoulder arthroplasty or rotator cuff repair. EXPAREL should be injected slowly (generally 1 to 2 mL per injection) with frequent aspiration to check for blood and minimize the risk of inadvertent intravascular injection. Do not exceed a maximum dosage of 133 mg (10 mL) for interscalene brachial plexus nerve block.

Can bupivacaine HCl be mixed with EXPAREL in a nerve block?

Bupivacaine HCl may be administered immediately before EXPAREL or admixed in the same syringe, as long as the ratio of the mg dose of bupivacaine HCl to EXPAREL does not exceed 1:2 (ie, 50% rule). Up to 75 mg of bupivacaine HCl may be added to EXPAREL 133 mg (10 mL).

Admixing EXPAREL with other drugs besides bupivacaine HCl prior to administration is not recommended. Some physicochemical incompatibilities exist between EXPAREL and certain other drugs. Nonbupivacaine-based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. Direct contact of EXPAREL with these drugs results in a rapid increase in free (unencapsulated) bupivacaine, altering EXPAREL characteristics and potentially affecting the safety and efficacy of EXPAREL.
Why should I not exceed a 1:2 ratio of bupivacaine to EXPAREL when admixing?

Bupivacaine HCl administered together with EXPAREL may impact the pharmacokinetic and/or physicochemical properties of EXPAREL, and this effect is concentration dependent. Therefore, when bupivacaine HCl and EXPAREL are administered simultaneously in the syringe or bupivacaine HCl is injected immediately before EXPAREL, the ratio of the milligram dose of bupivacaine HCl solution to EXPAREL should not exceed 1:2.

Back to questions

How do I factor in the amount of bupivacaine in EXPAREL into my weight-based bupivacaine calculations?

EXPAREL is not dosed by weight. The recommended dose of EXPAREL for an interscalene brachial plexus nerve block in adults is 133 mg (10 mL).

Back to questions

Can I administer other local anesthetics after using EXPAREL for interscalene brachial plexus nerve block?

Nonbupivacaine-based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of ≥20 minutes.

Furthermore, the toxic effects of local anesthetics are additive and their co-administration should be used with caution including monitoring for neurologic and cardiovascular effects related to local anesthetic systemic toxicity. The use of other local anesthetics with EXPAREL is NOT contraindicated. Additional use of local anesthetics should generally be avoided within 96 hours following administration of EXPAREL.

Clinicians should take into consideration the additive effects and the pharmacokinetics of other local anesthetics and should aim to maintain local anesthetic levels below their respective toxic levels.

Back to questions
Can a surgeon infiltrate with EXPAREL if an interscalene brachial plexus nerve block with EXPAREL is performed? In other words, can EXPAREL be used as infiltration and for interscalene brachial plexus nerve block in the same patient?

The maximum dose of EXPAREL a patient can receive is 266 mg. Therefore, a patient could receive EXPAREL 133 mg as an interscalene brachial plexus nerve block and EXPAREL 133 mg as a local infiltration. However, it should be noted that 10 mL of EXPAREL will not be sufficient to cover a large surgical site. EXPAREL 133 mg (10 mL) has only been studied in small surgical sites (eg, bunionectomy, oral surgery).5,6

Back to questions
EXPAREL is indicated for single-dose infiltration in adults to produce postsurgical local analgesia and as an interscalene brachial plexus nerve block to produce postsurgical regional analgesia. Safety and efficacy have not been established in other nerve blocks.

Important Safety Information

- EXPAREL is contraindicated in obstetrical paracervical block anesthesia.
- Adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration via infiltration were nausea, constipation, and vomiting; adverse reactions reported with an incidence greater than or equal to 10% following EXPAREL administration via interscalene brachial plexus nerve block were nausea, pyrexia, and constipation.
- If EXPAREL and other nonbupivacaine local anesthetics, including lidocaine, are administered at the same site, there may be an immediate release of bupivacaine from EXPAREL. Therefore, EXPAREL may be administered to the same site 20 minutes after injecting lidocaine.
- EXPAREL is not recommended to be used in the following patient population: patients <18 years old and/or pregnant patients.
- Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, EXPAREL should be used cautiously in patients with hepatic disease.

Warnings and Precautions Specific to EXPAREL

- Avoid additional use of local anesthetics within 96 hours following administration of EXPAREL.
- EXPAREL is not recommended for the following types or routes of administration: epidural, intrathecal, regional nerve blocks other than interscalene brachial plexus nerve block, or intravascular or intra-articular use.
- The potential sensory and/or motor loss with EXPAREL is temporary and varies in degree and duration depending on the site of injection and dosage administered and may last for up to 5 days, as seen in clinical trials.

Warnings and Precautions for Bupivacaine-Containing Products

- Central Nervous System (CNS) Reactions: There have been reports of adverse neurologic reactions with the use of local anesthetics. These include persistent anesthesia and paresthesia. CNS reactions are characterized by excitation and/or depression.
- Cardiovascular System Reactions: Toxic blood concentrations depress cardiac conductivity and excitability, which may lead to dysrhythmias, sometimes leading to death.
- Allergic Reactions: Allergic-type reactions (eg, anaphylaxis and angioedema) are rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients.
- Chondrolysis: There have been reports of chondrolysis (mostly in the shoulder joint) following intra-articular infusion of local anesthetics, which is an unapproved use.
- Methemoglobinemia: Cases of methemoglobinemia have been reported with local anesthetic use.

Please see the full Prescribing Information.

References